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Norman H. Stepno
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,953	BERNARD ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11 and 13-31* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,13-19 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/143,446* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

Claims 10-11 and 13-31 have been presented for examination.

Election/Restrictions

Applicant's election with traverse of Group I, claims 10-11, 13-19 and 25-31 in Paper No. 8, filed 04 November 2002 is acknowledged. The traversal is on the ground(s) that there is no burden. This is not found persuasive because burden was established by separate classification as set forth in MPEP 803 and the additional reasons set forth in the Office action of 07 October 1999 in parent application 09/143,446.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. It is suggested that the non-elected claims be canceled in response to this Office action to expedite prosecution.

Claim Rejections - 35 USC § 112

Claims 10-11, 13-19 and 25-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 25 and 27 recite "comprising" which is vague and indefinite because it is not clear how a compound, in this case, a polypeptide, can comprise anything other than itself.

Compositions can comprise multiple inert or unnecessary ingredients, but a compound is a discrete entity having well-defined properties.

In claims 10, 13, 25 and 27, it seems somewhat awkward to refer to the polypeptide at the same time as the protease. It is also unclear that there is a difference between "natural" and "synthetic" polypeptide. If this is a reference to the method of making, then "naturally occurring" and the means of "synthetic" making should be indicated. One can imagine both solid phase chemical as well as recombinant methods of making a protein which is not isolated from natural sources. It is not clear from the instant disclosure that applicants are in possession of a method of making the enzyme by chemical or recombinant means. No one has succeeded in making a protein of this size by chemical means, and recombinant means cannot be practiced without being in possession of the gene. As a consequence it is confusing as to what "synthetic" means.

In claims 10, 13, 25 and 27, a molecular weight range is required but without indicating the means by which the molecular weight was determined. It is well-known in the art that different means of measuring the molecular weight such as sedimentation, gel filtration, colligative methods, and SDS-PAGE will give different results and with different degrees of precision.

The range of molecular weight claimed in claims 10, 13, 25 and 27, to 15 to 32 kilodaltons, is quite broad compared to any known method of determining molecular weight. It is confusing that the mass of a discrete molecule could be reported to vary by over 100%.

Claim 10 recites "is a polypeptide fragment" which is vague and indefinite because the parent of the polypeptide fragment is not clear. Either the polypeptide is a cysteine protease, or it is not. This is very confusing.

Claim 25 is very confusing in that it is an inconsistent claim. The initial "paragraph" of the claim asserts a polypeptide that is a cathepsin L type cysteine protease with mass of 15 to 32 kDa, while the second "paragraph" of the claim asserts that the polypeptide is a complex having any structural or functional molecule attached to it. This makes no sense at all. A thing can't be something and something else at the same time. If this claim could be interpreted as claiming a complex with another molecule, it could be withdrawn from consideration as being drawn to a non-elected invention. This claim will be examined insofar as it reads on the elected invention, a cathepsin L type cysteine protease.

Claim 27 is very confusing in that it is an inconsistent claim. The initial "paragraph" of the claim asserts a polypeptide that is a cathepsin type L cysteine protease with mass of 15 to 32 kDa, while the second "paragraph" of the claim asserts that the polypeptide is an antibody or antisera prepared/purified from the protease. This makes no sense at all. A thing can't be something and something else at the same time. If this claim could be interpreted as claiming an antibody, it could be withdrawn from consideration as being drawn to a non-elected invention. This claim will be examined insofar as it reads on the elected invention, a cathepsin L type cysteine protease.

All of these claims are garbled in such a way as to make them nearly uninterpretable. It cannot be clearly determined what is being claimed: a protease? a fragment of a protease?, an antibody to the protease?, or a complex of the protease with some other macromolecule (is this covalent or noncovalent complex?). The claims will be examined insofar as they read on the elected invention, a cathepsin L type cysteine protease.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-11, 13-19, 25-31 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific cysteine protease, G4, does not reasonably provide enablement for fragments thereof or synthetic polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The instant claims assert fragments of a polypeptide having cathepsin L type cysteine protease activity. However, nowhere in the disclosure is there evidence that applicants are in possession of fragments of the isolated enzyme that possess cysteine protease activity. The disclosure has support for using the language. However, support is not enablement. The disclosure does not describe or indicate what fragments can be made, how they are made, or which amino acid residues can be removed, substituted or added to the subject polypeptide and still obtain an active cysteine protease. The disclosure does not describe any reproducible process of proteolyzing the subject protease so as to obtain active fragments thereof. It is critical that it is understood that the claims require that the fragments are active protease because dependent the claims depend from independent claims that describe the polypeptide as being a cathepsin L type cysteine protease. Absent guidance on the selection of appropriate residues to delete or

substitute, for example, and still retain the desired activity, a person of ordinary skill in the art would have to provide substantial inventive contribution to produce such a fragment. Such additional effort would clearly constitute undue burden.

Since the neither the sequence nor the gene encoding the subject polypeptide are disclosed, there is no evidence that applicants are in possession of sufficient information or skills to provide a synthetic form of the subject polypeptide. In fact, no one to date as succeeded in preparing a single polypeptide of this size by chemical means alone. Absent either the gene, sequence or evidence that the polypeptide can be made by synthetic means, a person of ordinary skill in the art would have to provide extraordinary additional contributions to obtain the enzyme by synthetic means. Such additional effort would clearly constitute undue burden.

Accordingly the claims are not commensurate in scope with the enabling disclosure with respect to fragments thereof or a synthetic form of the subject polypeptide.

Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain protease activator, does not reasonably provide enablement for any protease activator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

Claim 16 broadly asserts composition with any protease activator. Claim 17 sets forth a Markush group of activators, including urea. The scope of protease activators is quite broad and includes other proteases that activate by converting a proenzyme into the active enzyme (e.g., the blood clotting cascade). There is no evidence that the instant protease occurs as a proenzyme that

is in need of proteolytic activation. The instant disclosure provides basis for certain protease activators of the subject polypeptide: glycerol, EDTA, and reducing agents. It is said that one can "assimilate" transglutaminases with protease activators, but this statement is not understood. There is no basis for urea as a protease activator, and there is no evidence of record that it is known as such in the art. On the contrary, urea is known in the art as a chaotrope, and accordingly would be contraindicated as a protease activator. The basis of glycerol as a protease activator is tenuous at best. The disclosure recites, the "beneficial effect of glycerol on xeroses is, for example, known, which effect is explained by an activating effect on the enzymatic systems, due to its hydrating action through which it is thought to promote the action of proteases which break down the corneodesmosomes and hence the desquamation." Hence, the glycerol does not so much activate the enzyme as solubilize its substrate.

608.01(o) Basis for Claim Terminology in Description [R-14]

The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification with clear disclosure as to its import, and in mechanical cases it should be identified in the descriptive portion of the specification by reference to the drawing, designating the part or parts therein to which the term applies. A term used in the claims may be given a special meaning in the description. No term may be given a meaning repugnant to the usual meaning of the term.

Usually the terminology of the original claims follows the nomenclature of the specification, but sometimes in amending the claims or in adding new claims, new terms are introduced that do not appear in the specification. The use of a confusing variety of terms for the same thing should not be permitted.

In the instant case, protease activator appears to be used in a manner which is not consistent with art-accepted practice. This leads to some of the confusion. The disclosure conflates different properties as the same.

To determine if a particular agent is an activator of the subject polypeptide would have to be obtained on a case-by-case basis. There is no evidence that even all of the specified compounds are activators, let alone those unspecified. It would require considerable inventive contribution without any guidance at all to select additional protease activators. It is this additional experimentation that constitutes undue burden.

Accordingly the claims are not commensurate in scope with the enabling disclosure with respect to the selection of protease activators.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-11, 13-15, 25 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Kawada et al. (1997).

Kawada et al. (1997) disclose the isolation and characterization of a human cathepsin L protease from psoriatic epidermis. The initial form has a mass of 39 kDa by SDS-PAGE which subsequently matures into a single chain 30 kDa form which is further processed to two chains, a

25 kDa heavy chain and a 5 kDa light chain. Both the single chain and two chain forms are active. The pH optimum and pI are not reported.

Claims 10-11, 13-15, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Rao et al. (1995).

Rao et al. (1995) disclose cathepsin L from human gliomas having a mass of about 29 kDa. By means of antibodies to the enzyme, it was determined that the enzyme was present in normal brain but at higher levels in the tumor tissue.

Claims 10-11, 13-19, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Reilly et al. (1989) and claims 10-11, 13-15, 25 and 27 by Reilly et al. (1990).

Reilly et al. (1989) and Reilly et al. (1990) disclose a cathepsin L from human alveolar macrophages. The enzyme is synthesized as a 43 kDa precursor which is processed to a 34 kDa intermediate and subsequently to the mature form of 25 kDa. The enzyme is elastinolytic. The enzyme is said to have physical, catalytic and immunological properties identical with those reported for cathepsin L purified from human liver (page 495, column 1). The enzyme is purified into a 1 mM EDTA containing buffer in Reilly et al. (1989).

Claims 10-11, 13-15, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mason et al. (1984) and claims 10-11, 13-19, 25 and 27 by Mason et al. (1985).

Mason et al. (1984) and Mason et al. (1985) disclose the cathepsin L from human liver. The mass determined by SDS-PAGE (non-reduced) gave two poorly defined bands at 25 kDa

and 29 kDa. Upon reduction more clearly defined bands at 25 kD and 3.5 kD were seen. The 29 kDa species is said to be composed of two chains, 25 kDa and 5 kDa, linked by disulfides. Isoelectric focussing gave a major band at pH 5.9 with several minor bands in the range of 5.7-6.3 (page 238). The pH activity profile is provided in Fig. 2 of Mason et al. (1985), which shows that the enzyme is active over the range of 3-9 with an optimum of about 5.5-6.0. In Mason (1985) activity against azocasein in 3M urea was measured. The gene of the liver enzyme disclosed in Mason et al. (1986), Smith et al. (1989) and Gal et al. (1988) is consistent the mass assignments to the chains.

Claims 10-11, 13-19, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Baricos et al. (1988).

Baricos et al. (1988) disclose cathepsin L from human kidney. The mass determined by SDS-PAGE gave a band of 25-30 kD which upon reducing gives bands of 22-25 kD and 5-7 kD. The pH optimum was about 6.0 (page 302). Figure 1 shows incubation of the enzyme in 1 mM EDTA and 1mM DTT.

Claims 10-11, 13-15, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Chauhan et al. (1993).

Chauhan et al. (1993) disclose the genomic organization of human cathepsin L gene. The cDNA isolated from a cervical cancer cell line, a liver cell line and a kidney cell line have identical coding regions, although there are differences in the 5' noncoding region. Further

comparable properties of the enzyme are not provided. Hybridization analysis under low stringency of a total genomic library did not reveal other genes for this enzyme.

Claims 10-11, 13-15, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Uchiumi et al. (JP 06192124).

Uchiumi et al. (JP 06192124) disclose the precursor form of cathepsin L derived from human fibroblasts grown in cell culture. No physical properties are provided in the abstract. The molecular weight of the precursor appears to be about 37±3 kDa by SDS PAGE (paragraph 32). The amino terminal sequence of the precursor is provided in paragraph 35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-11, 13-19, 25 and 27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kawada et al. (1997), Rao et al. (1995), Mason et al. (1984), Mason et al. (1985), Baricos et al. (1988), Chauhan et al. (1993) and Uchiumi et al. (JP 06192124).

A person of ordinary skill in the art at the time the invention was made would have been motivated to obtain cathepsin L from human epidermis having a pI of 6-9, a mass of 25-30 kD and a pH optimum of 3.5-6.5 in view of the teachings of Kawada et al. (1997), Rao et al. (1995), Mason et al. (1984), Mason et al. (1985), Baricos et al. (1988), Chauhan et al. (1993) and

Uchiumi et al. (JP 06192124) because taken as a whole these references reasonably suggest that there is only one cathepsin L in human tissues which is produced in a precursor form of about 43 kD and processed through an intermediate form of about 34 kD to a final mature two chain form of about 29 kD which can be separated under reducing conditions into chains having masses of 25 kD and 5 kD. The enzyme from liver and kidney have been demonstrated to have the same coding sequence, albeit two different cDNAs have been identified (indicated to be possibly splicing variants in the 5'-noncoding region), the enzyme from alveolar macrophages is said to have the same kinetic, physical and immunological properties as the liver enzyme. The disclosed properties of the cathepsin L from glioma and brain, psoriatic epidermis and fibroblasts are comparable to the properties of the liver/kidney/macrophage enzyme. The liver cathepsin L has been the most extensively studied because it has been cloned for some time and suitable quantities of the enzyme are available. The reported value of the pI of the liver enzyme is 5.9, and liver enzyme is active over the pH range of 3-9 with an optimum of about 5.5-6.0. Genetic evidence suggests that there is only one gene coding for this enzyme.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to obtain the same cathepsin L from human epidermis as was obtained from various other human tissues. Although the properties of the cathepsin L obtained from human psoriatic epidermis and from human fibroblasts are not disclosed in the relied upon references, it can be reasonably suggested that the enzyme from the same tissue as instantly disclosed is the same as obtained from all of the other tissues: kidney, liver, brain, glioma, and macrophage.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
December 23, 2002